



Effect of an Early Dose of Measles Vaccine on Morbidity Between 18 Weeks and 9 Months of Age: A Randomized, Controlled Trial in Guinea-Bissau

Do, Vu An; Biering-Sorensen, Sofie; Fisker, Ane Bærent; Balé, Carlito; Rasmussen, Stine Møller; Christensen, Lone Damkjær; Jensen, Kristoffer Jarlov; Martins, Cesário; Aaby, Peter; Benn, Christine Stabell

Published in:
Journal of Infectious Diseases

Link to article, DOI:
[10.1093/infdis/jiw512](https://doi.org/10.1093/infdis/jiw512)

Publication date:
2017

Document Version
Publisher's PDF, also known as Version of record

[Link back to DTU Orbit](#)

Citation (APA):
Do, V. A., Biering-Sorensen, S., Fisker, A. B., Balé, C., Rasmussen, S. M., Christensen, L. D., Jensen, K. J., Martins, C., Aaby, P., & Benn, C. S. (2017). Effect of an Early Dose of Measles Vaccine on Morbidity Between 18 Weeks and 9 Months of Age: A Randomized, Controlled Trial in Guinea-Bissau. *Journal of Infectious Diseases*, 215(8), 1188-1196. <https://doi.org/10.1093/infdis/jiw512>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Effect of an Early Dose of Measles Vaccine on Morbidity Between 18 Weeks and 9 Months of Age: A Randomized, Controlled Trial in Guinea-Bissau

Vu An Do,^{1,2,a} Sofie Biering-Sørensen,^{1,2,a} Ane Bærent Fisker,^{1,2} Carlito Balé,² Stine Møller Rasmussen,^{1,2} Lone Damkjær Christensen,^{1,2} Kristoffer Jarlov Jensen,^{1,3} Cesário Martins,² Peter Aaby,² and Christine Stabell Benn^{1,4}

¹Research Center for Vitamins & Vaccines (CVIVA), Bandim Health Project, Statens Serum Institut, Artillerivej 5, DK-2300 Copenhagen S, Denmark; ²Projeto de Saúde Bandim, INDEPTH Network, Codex 1004, Bissau, Guinea-Bissau; ³Section for Immunology and Vaccinology, National Veterinary Institute, Technical University of Denmark, Bülowsvej 27, DK-1870 Frederiksberg C, and ⁴Odense Patient data Explorative Network, Institute of Clinical Research, University of Southern Denmark/Odense University Hospital, J.B. Winslows Vej 9a, DK-5000 Odense C, Denmark

(See the editorial commentary by Flanagan on pages 1177–8 and major article by Woudenberg et al on pages 1181–8.)

Background. Children in Guinea-Bissau receive measles vaccine (MV) at 9 months of age, but studies have shown that an additional dose before 9 months of age might have beneficial nonspecific effects. Within a randomized trial designed to examine non-specific effects of early MV receipt on mortality, we conducted a substudy to investigate the effect of early MV receipt on morbidity.

Methods. Children were randomly assigned at a ratio of 2:1 to receive 2 doses of MV at 18 weeks and age 9 months (intervention group) or 1 dose of MV at age 9 months, in accordance with current practice (control group). Children were visited weekly from enrollment to age 9 months; the mother reported morbidity, and the field assistants examined the children. Using Cox and binomial regression models, we compared the 2 randomization groups.

Results. Among the 1592 children, early measles vaccination was not associated with a higher risk of the well-known adverse events of fever, rash, and convulsions within the first 14 days. From 15 days after randomization to age 9 months, early measles vaccination was associated with reductions in maternally reported diarrhea (hazard ratio [HR], 0.89; 95% confidence interval [CI], .82–.97), vomiting (HR, 0.86; 95% CI, .75–.98), and fever (HR, 0.93; 95% CI, .87–1.00).

Conclusion. Early MV receipt was associated with reduced general morbidity in the following months, supporting that early MV receipt may improve the general health of children.

Keywords. measles vaccine; adverse events; morbidity; non-specific effects of vaccines; heterologous immunity; pediatric.

Vaccines are designed to induce immunity to specific diseases, but research has shown that vaccines may yield so-called non-specific effects (NSEs) involving altered susceptibility to a variety of infectious diseases other than those targeted by the vaccine. Live vaccines, such as measles vaccine (MV) and oral polio vaccine (OPV), may have beneficial NSEs and reduce overall mortality beyond what is expected from protection against their target diseases [1–4]. In contrast, inactivated vaccines, such as diphtheria-tetanus-pertussis (DTP) vaccine, despite providing protection against the target diseases, have been associated with increased overall mortality [5, 6].

The beneficial NSEs of MV have been tested in a randomized trial in Guinea-Bissau. In low-income countries, the World

Health Organization (WHO) recommends receiving MV at 9 months of age. This guideline is a compromise between avoiding interference with maternal antibodies, which reduce the antibody response to MV, and minimizing the risk of acquiring early measles virus infection [7]. The Bandim Health Project (BHP) in Guinea-Bissau conducted a randomized trial (during 2003–2007) to test the NSEs of early MV receipt [1]. Children aged 4.5 months were enrolled and followed until 36 months of age. The intervention group received 2 doses of MV (an early dose at 4.5 months of age and the recommended dose at 9 months of age). The control group received only the recommended dose at 9 months of age. The study showed a 22% reduction (95% confidence interval [CI], –5%–41%) in mortality before 36 months of age in the intervention group, in the intention-to-treat analysis. Many children had also been enrolled in a trial of neonatal vitamin A supplementation (NVAS); among children not receiving NVAS at birth, early MV receipt was associated with a 41% reduction (95% CI, 11%–61%) in mortality between 4.5 and 36 months of age; in children who had received NVAS, the effect of MV receipt was a 7% higher (95% CI, –29%–61%) mortality risk [1]. The effect of early MV receipt was also seen for hospital admission, in which early MV receipt was associated with a significant reduction in all-cause hospitalizations between 4.5 and 9 months of age [8]. This was

Received 29 June 2016; accepted 18 October 2016.

^aV. A. D. and S. B.-S. are co-first authors.

Correspondence: K. J. Jensen, Research Center for Vitamins and Vaccines, Bandim Health Project, Statens Serum Institut, Artillerivej 5, DK-2300 Copenhagen S, Denmark (kjj@ssi.dk).

The Journal of Infectious Diseases® 2017;215:1188–96

© The Author 2017. Published by Oxford University Press for the Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, contact journals.permissions@oup.com. DOI: 10.1093/infdis/jiw512

consistent with findings of another study, which indicated that MV reduced non-measles-related mortality among hospitalized children in Guinea-Bissau [9].

We do not know whether early MV receipt also affects the incidence of less serious morbidities for which children are not hospitalized. In 2011, when children no longer received NVAS, the BHP initiated a randomized trial examining the effect of 2 doses of MV at 18 weeks and 9 months of age (intervention) versus 1 dose of MV at 9 months of age (control). A substudy was initiated to test whether early MV receipt reduced general morbidity up to 9 months of age, when all children received MV. We also investigated adverse events in connection with early MV receipt. The results from the substudy are presented in the present article.

METHODS

Setting and Study Population

The BHP in Guinea-Bissau maintains a health and demographic surveillance system in the capital, Bissau. The study area covers 6 districts with around 100 000 inhabitants. Three health centers in the study area provide routine vaccinations, and BHP registers all vaccines given to children living in the study area. A field team visits all houses once monthly to record new pregnancies and births.

Main Trial Design

The main trial was initiated in August 2011. Children were randomly assigned to receive either 2 doses of MV at 18 weeks and 9 months of age (the intervention group) or the recommended single dose of MV at 9 months of age (the control group). The BHP identified all newborn children in the study area and reminded the mothers to bring their children for vaccination at the health centers. Children in Guinea-Bissau receive pentavalent vaccine (targeting DTP, hepatitis B, and *Haemophilus influenzae* type b infection) at 6, 10, and 14 weeks of age [10]. Children between 18 weeks and 7 months of age, who had received the third and last dose of pentavalent vaccine at least 4 weeks earlier, were eligible to be enrolled in the trial. NVAS was not given during the study. There were no reports of circulating measles virus during the trial; the last measles epidemic in Bissau was in 2003–2004.

When the child was ready to be enrolled, the mother/guardian was invited to come to the health center. At the health center, the mother/guardian received an explanation of the study in the local language, Creole, and a written explanation in the official language, Portuguese. Anthropometric measurements of the child were performed, and a clinical examination conducted by a physician. Provided the mother agreed to participate, she was asked to sign or fingerprint a consent form. The mother then drew a numbered lot from an envelope to randomly assign the child to the intervention or control group, using block randomization stratified by sex (block size, 24; randomization ratio,

2:1 for the intervention group to the control group). The vaccine used was a standard-titer Edmonston-Zagreb MV from the Serum Institute of India. Placebo was not used, as mothers may erroneously believe that their child received MV and not seek MV when their child reached 9 months of age. Children with physical malformations or with severe malnutrition (mid-upper-arm circumference, <115 mm) were excluded and referred for treatment. Overly sick children were not invited to participate but, instead, were referred to consultation at the health center; the mother and her child were invited back for enrollment once the child had recovered.

Morbidity Substudy Design

The substudy of morbidity was initiated in October 2011, and the last child was enrolled in June 2013. For logistic reasons, a maximum of 5 children were enrolled every day; if >5 children were eligible, the 5 youngest were selected. Children enrolled in the substudy were followed with weekly morbidity interviews between enrollment and 9 months of age. Trained field assistants who were unaware of the child's randomization status conducted interviews with the mother. The first weekly visit with a child took place 6 days after enrollment, and the field assistant would explain the purpose and the procedures of the weekly visits. To give the mother a better understanding of the symptoms, we gave them a flyer with custom-made illustrations of the symptoms. At the weekly visits, the field assistants asked about the following symptoms during each of the past 7 days (with the day of visit included): diarrhea, vomiting, cough, lack of appetite, crying more than usual, fever, and convulsions. Furthermore, the assistant asked whether the mother had taken the child for consultation or given the child medicine. If any medication was administered during the past 7 days, the mother was asked to show the medication, and the type of medication was recorded. In addition to the interview, on the day of the visit the assistant registered whether skin reactions, conjunctivitis, and nasal discharge were present and measured the child's axillary temperature. If the field assistant encountered a sick child, the child was referred for consultation. If a child had moved within the BHP catchment area, the field assistant would immediately try to visit the new house. Follow-up for a child would terminate if the child moved outside the study area.

Definition of Possible Adverse Events

Adverse events associated with MV were defined as fever, convulsions, and skin reactions. Fever may occur around days 5–12 after MV receipt, and the risk of febrile seizures increases around day 8–14 [11]. Fever was defined as an axillary temperature of >37.0°C. MV-associated adverse events affecting the skin were defined as generalized exanthema, which occurs around day 7–10 after vaccination [11]. To have a period in which most adverse events would be captured, we analyzed adverse events from days 5 to 14.

Definition of General Morbidity

We expected that children randomly assigned to the intervention group would have a higher incidence of adverse events in the first 14 days after enrollment in the study [12]. Hence, the potential NSEs of early MV receipt were assessed from day 15 after enrollment to 9 months of age. Fever was, as in the analyses on possible adverse events, defined as an axillary temperature of $>37.0^{\circ}\text{C}$. Skin reaction was defined as generalized exanthema, abscess, or localized rash.

Statistical Analyses

Adverse Events

We used log-binominal regression to estimate prevalence ratios and 95% CIs for potential adverse events in comparisons of the intervention and control groups.

General Morbidity

Maternally reported and assistant-observed symptoms were analyzed using Cox regression, with time since randomization as the underlying time, to provide hazard ratios (HRs) with 95% CIs for comparison of the intervention and control groups. Use of age as the underlying time did not affect the results. Data were analyzed as a multiple failure time data set. For maternally reported symptoms, symptoms were registered daily. Symptoms extending over consecutive days contributed only 1 episode; if symptoms returned after 1 symptom-free day, it constituted a new episode. For the weekly observations by the field assistant, multiple events over consecutive visits were treated as separate events, except for skin reactions, which were treated as 1 event if multiple episodes were observed. We made this decision because of the long-lasting character of skin reactions and, therefore, the higher likelihood that the manifestation of symptoms in the skin observed during 2 consecutive visits constitutes the same episode.

All analyses were stratified by sex because early MV receipt may have sex-differential effects [13]. Furthermore, the previous trials of early MV receipt have shown that mortality is reduced if MV is administered in the presence of measles virus maternal antibodies, as compared to vaccination in the absence of maternal antibodies [14]. Children who are younger will have more antibodies, and we therefore conducted an analysis stratified by age at inclusion, using a cutoff of 140 days (20 weeks, or 4.5 months) of age (ie, <20 weeks vs ≥ 20 weeks).

As prespecified in the study protocol, we examined whether the estimated effect of early MV receipt was influenced by other vaccinations. The only vaccination given during follow-up was OPV, during national campaigns targeting all children present during the campaign. We subdivided the follow-up time into time before OPV campaigns and time after OPV campaigns. OPV campaigns were conducted in November 2011, March 2012, and May 2013. The first analysis, “before OPV campaign,” consisted of follow-up before the first day of OPV campaigns, and the second analysis, “after OPV campaign,” consisted of follow-up after the OPV

campaigns. Hence, events that occurred during an OPV campaign have not been included in these analyses.

Stata, version 11, was used for the statistical analyses. Data can be obtained for further analysis through contact with the authors.

Ethical Considerations

The BHP offered free healthcare consultations and essential drugs to all participants. The Guinean Ministry of Health’s Research Coordination Committee approved the protocol, and we obtained consultative approval from the Danish Central Ethical Committee. The study was registered at clinicaltrials.gov (NCT01486355).

RESULTS

Over a study period of 20 months, 3117 children were eligible for enrollment into the morbidity subgroup study (Figure 1); since we could only enroll 5 children per day for the morbidity study, 1625 were included in this substudy. There were no significant differences between the 1625 participants and the 1492 nonparticipants at enrollment, except with regard to age, weight, and height, which were all lower among participants because we selectively invited the youngest children if >5 children were eligible per day (data not shown). In the follow-up period, 3 children were not found at home at any visits, 16 were traveling throughout the follow-up period, 4 had moved before any follow-up data had been obtained, and forms for 10 were lost. These children were excluded from the analyses. One child had received MV elsewhere and was censored on the day they received the MV. There were no differences in baseline characteristics between the intervention and control groups (Table 1). For all enrolled children, 77% of all attempted follow-up visits were successful, with the mother/guardian and child found at home (frequency of successful follow-up, 76% in the intervention group, and 77% in the control group).

Possible Adverse Events Associated With Early MV Receipt

Overall and stratified by sex, there was no effect of early MV receipt on possible adverse events (Table 2). As expected, there was a tendency toward a higher frequency of measured fever at day 7 among children in the intervention group. However, for maternally reported fever in children, this tendency was opposite.

General Morbidity

Maternally Reported Symptoms

Early MV receipt was associated with a lower hazard for diarrhea (HR, 0.89; 95% CI, .82–.97), vomiting (HR, 0.86; 95% CI, .75–.98), and reported fever (HR, 0.93; 95% CI, .87–1.00; Table 3). The remaining symptoms also tended to be less common in the intervention group. Stratified by sex, the beneficial effect of early MV receipt on morbidity was generally stronger in boys, compared with girls. Boys who received MV early had a reduced risk of diarrhea (HR, 0.87; 95% CI, .78–.98), vomiting (HR, 0.78; 95% CI, .66–.92), coughing (HR, 0.88; 95% CI,

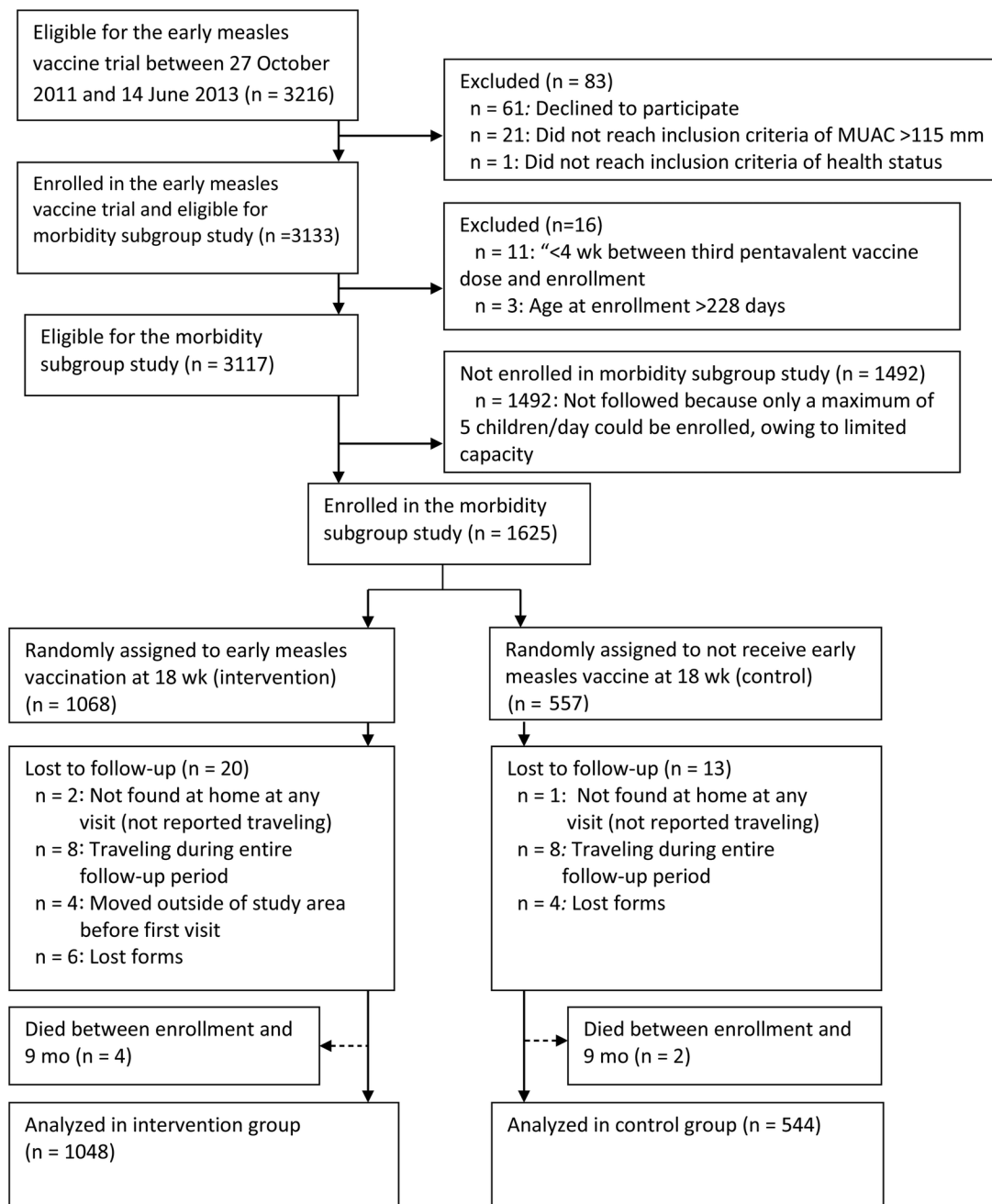


Figure 1. Flow of participant through the study. Infants who died between enrollment and 9 months were included in the analyzes, but censored at time of the last visit seen alive. Abbreviation: MUAC, mid-upper-arm circumference.

.80–.98), and reported fever (HR, 0.89; 95% CI, .82–.98; Figure 2 and Supplementary Data), compared with control boys. For coughing and crying more than normal, there was an interaction between sex and early MV receipt (coughing, $P = .02$; crying more than normal, $P = .01$).

Field Assistant Observations at Home Visit

Early MV receipt was associated with a reduced risk of skin reactions (HR, 0.76; 95% CI, .60–.95; Table 3). Stratified by sex, early MV receipt was associated with a decreased risk of skin

reactions in boys (HR, 0.59; 95% CI, .43–.81) but not in girls (HR, 0.99; 95% CI, .71–1.40; $P_{\text{interaction}} = 0.03$; Figure 2 and Supplementary Data).

Age at Inclusion

When we stratified analysis by age at inclusion, children included at <20 weeks of age and randomly assigned to the intervention group had lower hazards of coughing (HR, 0.86; 95% CI, .76–0.97), lack of appetite (HR, 0.74; 95% CI, .59–.93), reported fever (HR, 0.84; 95% CI, .76–.94), measured fever (HR, 0.74;

Table 1. Baseline Characteristics of Children Enrolled in the Morbidity Subgroup Study and Randomly Assigned to Receive (Intervention) or Not Receive (Control) an Early Dose of Measles Vaccine at 18 Weeks of Age

| Characteristic | Intervention (n = 1068) | Control (n = 557) |
|----------------------------------|----------------------------|----------------------|
| Sociodemographic | | |
| Age at enrollment, wk | 21.1 (19.7–21.7) | 21.1 (19.7–21.7) |
| Age of mother at enrollment, y | 26 (21–30) | 26 (22–30) |
| Male sex | 53 (563) | 53 (295) |
| Living in Bandim district | 42 (447) | 45 (249) |
| Toilet inside house | 22 (235) | 23 (130) |
| Anthropometry | | |
| Weight, kg, mean \pm SD | 7.2 \pm 1.0 | 7.2 \pm 1.0 |
| Height, cm, mean \pm SD | 63.2 \pm 2.5 | 63.2 \pm 2.5 |
| MUAC, mm, mean \pm SD | 141 \pm 12 | 142 \pm 11 |
| Maternal MUAC, mm, mean \pm SD | 280 \pm 38 | 281 \pm 36 |
| Morbidity | | |
| Diarrhea at enrollment | 9 (97) | 12 (66) |
| Coughing at enrollment | 32 (338) | 34 (191) |
| Hospitalized before enrollment | 5 (54) | 5 (30) |
| Risk factor at enrollment | | |
| No. of people/bed | 2.8 (2–3) | 2.9 (2–3) |
| No. of people/sleeping room | 4.3 (3–5) | 4.2 (3–5) |

Data are % (no.) of subjects or mean value (interquartile range), unless otherwise indicated. Abbreviation: MUAC, mid-upper-arm circumference.

95% CI, .60–.89), and crying more than normal (HR, 0.74; 95% CI, .61–.89), compared with children in the control group. For each of these symptoms, we found a significant interaction ($P < .05$) between age at inclusion and early MV receipt. The reverse tendency, with early MV receipt being associated with a lower risk for children included at ≥ 20 weeks of age, was seen for diarrhea (HR, 0.83; 95% CI, .75–.93) and vomiting (HR, 0.83; 95% CI, .71–.98); for diarrhea, this resulted in a significant interaction between age and early MV receipt (Figure 3 and [Supplementary Data](#)).

Effect Modification by OPV Campaigns

We subdivided the follow-up time into time before OPV campaigns and time after OPV campaigns and found a significantly reduced risk of maternally reported diarrhea and vomiting in the group that received MV early, before OPV campaigns. There was no significant effect modification by OPV campaign, however, for any of the outcomes ([Supplementary Figure 1 and Supplementary Data](#)).

DISCUSSION

We did not find statistically significant differences between the 2 randomized groups when looking at possible adverse events. We found a reduced risk of maternally reported and assistant-observed morbidity in the intervention group. The beneficial effect of early MV receipt was stronger in boys, compared with girls, and tended to be stronger in the youngest group of children.

For logistic reasons, we were only able to include 5 children per day. Therefore participants differed from nonparticipants with respect to age, weight, and height, but otherwise there were no differences between participants and nonparticipants. All background factors were evenly distributed between the intervention and control groups. The follow-up was based on data from home visits, and the loss to follow-up was limited. Furthermore, the assistants were trained in a uniform way by the same supervisor, with regard to both interview technique and health observations. We did not use placebo. However, early MV receipt was not registered on the health card, and the field assistants were not aware of the randomization status, nor were the physicians or nurses conducting consultations and prescribing medicine. The mothers of the enrolled children were not blinded, which could have led to a bias in the reporting of symptoms. However, the results for consultation and use of medicine and the symptoms observed by the field assistants were in the same direction, supporting that the maternally reported symptoms were not due to the mothers' awareness of the randomization status.

The study reported 12 primary analyses and 36 secondary analyses of an effect of early MV receipt on morbidity, entailing a risk of chance findings. The results should therefore be interpreted with this in mind.

There was no circulating measles virus in Bissau in the preceding 2–3 years; the last measles epidemic in Bissau was in 2003–2004 [1]. During the study, we had a system of measles surveillance, consisting of field assistants going to all houses once monthly to ask for measles cases, as well as daily reporting of potential measles cases from the health centers and the main hospital of Bissau. No measles case was found in the study area during the study, and we therefore believe the beneficial effect of early MV receipt on morbidity is due to NSEs, contradicting a recent hypothesis suggesting that the beneficial effects of MV are due to its prevention of measles-associated immunological memory loss [15].

The WHO recently reviewed the potential NSEs of vaccines in both observational and randomized trials. It concluded that there was evidence that MV reduced the risk of all-cause mortality independently of its effect on measles-attributable mortality [16]. The present trial corroborates the results of the WHO review by finding a beneficial effect of early MV receipt on morbidity. Furthermore, in the previous trial of early MV receipt, early receipt at 4.5 months of age reduced the risk of hospitalizations for respiratory infections between 4.5 and 9 months of age, compared with the group receiving MV only at 9 months of age [8]. Likewise, a study from the pediatric ward in Guinea-Bissau showed that receipt of MV reduced the risk of death from pneumonia [9].

A Danish study recently analyzed the effect on hospital admissions of having the measles-mumps-rubella vaccine (MMR) as compared to the inactivated DTP (ie, DTaP)/

Table 2. Risk of Adverse Events During the First 2 Weeks After Random Assignment to Receive (Intervention) or Not Receive (Control) an Early Dose of Measles Vaccine at 18 Weeks of Age

| Variable | Overall | | | Boys | | | Girls | | |
|---|--|----------------------|---------------------------------------|--|----------------------|---------------------------------------|--|----------------------|---------------------------------------|
| | No. of Events/Person-Year of Observation | | | No. of Events/Person-Year of Observation | | | No. of Events/Person-Year of Observation | | |
| | Intervention (n = 1048) | Control (n = 544) | Hazard Ratio ^a (95% CI) | Intervention (n = 551) | Control (n = 287) | Hazard Ratio ^a (95% CI) | Intervention (n = 497) | Control (n = 257) | Hazard Ratio ^a (95% CI) |
| Maternally reported adverse events, days 5–14 | | | | | | | | | |
| Fever day | 11.5 (226/20) | 13.7 (141/10) | 0.83 (.68–1.03) | 12.3 (127/10) | 14.7 (79/5) | 0.83 (.63–1.10) | 10.7 (99/10) | 12.7 (62/5) | 0.84 (.61–1.15) |
| Convulsions | 0.0 (0/21) | 0.0 (0/11) | ... | 0.0 (0/11) | 0.0 (0/6) | ... | 0.0 (0/10) | 0.0 (0/5) | ... |
| Assistant-observed adverse events, day 7 | | | | | | | | | |
| Present, day 7 ^c | 81.7 (868) | 81.4 (450) | | 83.3 (465) | 81.6 (239) | | 80.0 (403) | 81.2 (211) | |
| Measured fever ^d | 4.2 (36) | 3.6 (16) | 1.17 (.65–2.08) | 4.5 (21) | 4.2 (10) | 1.08 (.52–2.25) | 3.7 (15) | 2.8 (6) | 1.31 (.52–3.32) |
| Generalized exanthema ^d | 1.0 (9) | 2.0 (9) | 0.52 (.21–1.30) | 1.5 (7) | 2.5 (6) | 0.60 (.20–1.76) | 0.5 (2) | 1.4 (3) | 0.35 (.06–2.08) |
| Assistant-observed adverse events, day 14 | | | | | | | | | |
| Present, day 14 ^c | 81.3 (862) | 82.6 (457) | | 82.1 (457) | 81.9 (240) | | 80.5 (405) | 83.5 (217) | |
| Measured fever ^d | 4.8 (41) | 4.8 (22) | 0.99 (.60–1.64) | 5.5 (25) | 6.3 (15) | 0.88 (.47–1.63) | 4.0 (16) | 3.2 (7) | 1.23 (.51–2.94) |
| Generalized exanthema ^d | 0.7 (6) | 1.5 (7) | 0.45 (.15–1.35) | 1.1 (5) | 2.5 (6) | 0.44 (.14–1.42) | 0.3 (1) | 0.5 (1) | 0.54 (.03–8.52) |

Abbreviation: CI, confidence interval.

^a Determined using Cox regression, with time since randomization as the underlying time.

^b Determined using log-binomial regression.

^c Data are % (no.) of the total children included.

^d Data are % (no.) of the assessed children.

Table 3. Effect of Early Measles Vaccine Receipt on Maternally Reported and Assistant-Observed Morbidity After Random Assignment to Receive (Intervention) or Not Receive (Control) an Early Dose of Measles Vaccine

| | Morbidity Rate (No. of Events/Person-Years of Observation) | | |
|-------------------------------|--|-------------------|------------------------------------|
| Variable | Intervention (n = 1048) | Control (n = 544) | Hazard Ratio ^a (95% CI) |
| Maternally reported morbidity | | | |
| Diarrhea | 6.0 (1397/233) | 6.7 (805/120) | 0.89 ^b (.82–.97) |
| Vomiting | 2.5 (598/241) | 2.9 (358/124) | 0.86 ^b (.75–.98) |
| Coughing | 9.4 (1929/206) | 9.7 (1018/105) | 0.96 (.89–1.04) |
| Lack of appetite | 2.2 (525/236) | 2.4 (290/121) | 0.93 (.80–1.07) |
| Crying more than normal | 3.5 (820/237) | 3.5 (431/122) | 0.98 (.87–1.10) |
| Reported fever | 10.1 (2316/228) | 10.9 (1273/117) | 0.93 ^b (.87–1.00) |
| Reported consultations | 4.4 (1080/244) | 4.4 (557/126) | 1.00 (.90–1.11) |
| Reported use of medicine | 8.8 (1894/214) | 9.2 (1017/110) | 0.96 (.89–1.04) |
| Assistant-observed morbidity | | | |
| Skin reaction ^c | 5.5 (185/34) | 7.1 (124/18) | 0.76 ^b (.60–.95) |
| Conjunctivitis | 4.6 (156/34) | 4.1 (72/18) | 1.13 (.86–1.49) |
| Nasal discharge | 93.1 (3171/34) | 96.1 (1686/18) | 0.97 (.91–1.03) |
| Measured fever | 19.4 (662/34) | 21.7 (381/18) | 0.90 (.79–1.02) |

Events occurring from day 15 after random assignment through 9 months of age were included in the analysis. Maternally reported symptoms were registered per day. Symptoms extending over consecutive days contributed only 1 episode, and the person-years reported in the table are therefore symptom specific.

Abbreviation: CI, confidence interval.

^a Determined using Cox regression, with time since randomization as the underlying time.

^b $P < .05$ for the comparison between the intervention and control groups.

^c Defined as generalized exanthema (n = 139 events), abscess (n = 70 events), or localized rash (n = 100 events).

inactivated polio/*H. influenzae* type b vaccine as the latest vaccine. The study found a reduced risk of admissions for all types

of infection when MMR was the latest vaccine received, and particularly so for lower respiratory tract infections [17]. This is consistent with the present study, in which we found a

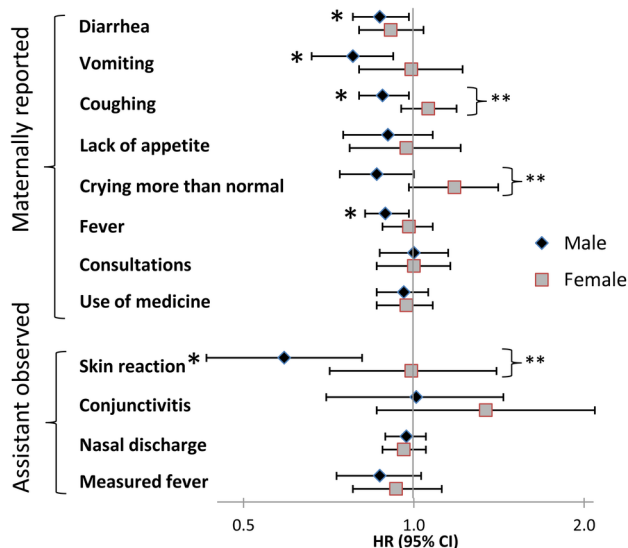


Figure 2. The effect of early measles vaccine receipt (intervention) on maternally reported and assistant-observed morbidity, stratified by sex. Hazard ratios (HRs) with 95% confidence intervals (CIs; whiskers) for maternally reported and assistant-observed morbidity were determined using Cox regression, with time since randomization as the underlying time, to compare the intervention group to the group that did not receive an early dose of measles vaccine (control). For maternally reported symptoms, symptoms were registered per day. Symptoms extending over consecutive days contributed only 1 episode. * $P < .05$ for comparison of the intervention and control groups; ** $P < .05$ for interaction between sex and early measles vaccine receipt.

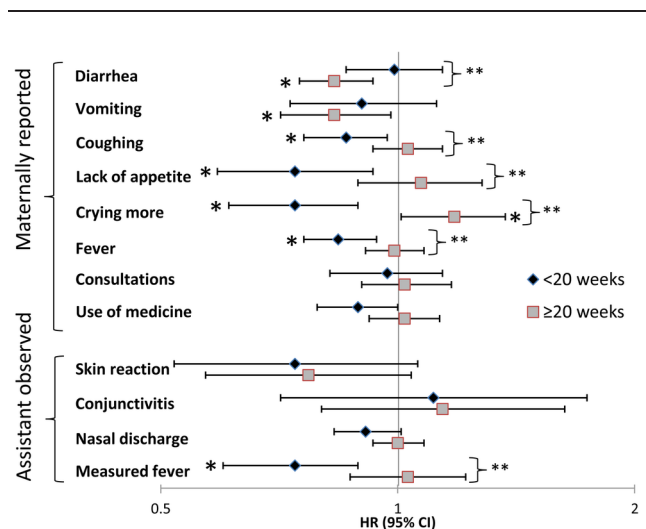


Figure 3. The effect of early measles vaccine receipt (intervention) on maternally reported and assistant-observed morbidity, stratified by age at inclusion. Hazard ratios (HRs) with 95% confidence intervals (CIs; whiskers) for maternally reported and assistant-observed morbidity were determined using Cox regression, with time since randomization as the underlying time, to compare the intervention group to the group that did not receive an early dose of measles vaccine (control). For maternally reported symptoms, symptoms were registered per day. Symptoms extending over consecutive days contributed only 1 episode. * $P < .05$ for comparison of the intervention and control groups; ** $P < .05$ for interaction between age at enrollment and early measles vaccine receipt.

reduced risk of fever and a tendency toward a reduced risk of coughing, which reached significance in males and in children enrolled before 20 weeks of age. In line with our findings of reduced risks of diarrhea and vomiting, the Danish study [17] also found a reduced risk of admissions for gastrointestinal infections. It should be noted that these studies of the NSEs of MV/MMR have mainly compared MV recipients to children for whom DTP-containing vaccine was the most recent vaccine received. Because DTP-containing vaccine has been associated with increased overall mortality and morbidity [5, 17], it cannot be excluded that the observed beneficial effect of MV is partly a consequence of an excess mortality and morbidity in the DTP-vaccinated control group.

We found a tendency toward a stronger beneficial effect in boys as compared to girls. These sex-differential effects are inconsistent with previous observations, in which girls benefitted more from MV [1, 8, 13, 18]. However, we have previously shown that there is a benefit from receiving MV in the presence of maternal antibody [14]. We have also previously shown that girls lose maternal antibodies faster than boys [19]; as more and more mothers are vaccinated and children receive less maternal measles antibody, girls would be most affected. Hence, this could potentially explain why the boys benefitted more in the present study than in previous studies.

In line with the literature on adverse events after MV receipt, we found an increased risk of measured fever among children in the intervention group during the 2 weeks after immunization [11].

Little is known about the immunological mechanisms behind the NSEs of MV. The observation that vaccines modify the immunological response to nonrelated pathogens is documented for BCG, which increases the innate responsiveness via epigenetic reprogramming of monocytes [20]. Whether MV acts via a similar mechanism is not known. The limited data available on the nonspecific immune activation of MV are somewhat conflicting, as studies indicate that MV transiently decreases [21–23] or increases [24, 25] the response potential of lymphocytes. Some studies indicate that MV skews immune reactions toward a T-helper type 1–biased profile in infants [21, 24], which may affect responses to subsequent pathogens and vaccines. Moreover, MV may carry cross-reactive epitopes potentially conferring immunity to heterologous pathogens, including respiratory syncytial virus (RSV) [26], a prominent cause of infections in the present study population [27]. To that end, the observed reduction in fever and coughing may be related to reduced incidence or severity of RSV infection, as also suggested in a study of hospital contacts among young Danish children [28].

To our knowledge, this is the first study to examine continuous subsequent morbidity after receiving an MV dose earlier than recommended. The outcomes of the present study indicate a decreased hazard of morbidity after early MV receipt, at 18 weeks of age, and add to the existing evidence supporting that

an early 2-dose MV strategy has beneficial NSEs. Although the WHO recommends a 2-dose vaccination strategy for MV for all national immunization programs, 9 months is the recommended age for the first dose, and 15–18 months is the age recommended for the second dose [29]. In countries with low rates of measles, the first dose may be administered even later than 9 months. However, based on the current evidence, it seems that recommending a standard dose of MV at 18 weeks of age could decrease mortality and morbidity in a low-income setting such as Guinea-Bissau.

Supplementary Data

Supplementary materials are available at <http://jid.oxfordjournals.org>. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

Acknowledgments. The research group thanks the mothers and children participating in the trial. We thank the staff at Bandim Health Project, the partners at the health centers in the study area, and, for supervising the statistical analyses, Andreas Andersen.

C. S. B., P. A., and C. M. were the chief investigators of the main measles trial. V. A. D., S. B. S., A. B. F., C. S. B., and P. A. designed the morbidity substudy. V. A. D. and S. B. S. initiated the study routines. V. A. D. was responsible for the recruitment and follow-up for participants, with help from S. B. S., S. M. R., and C. B. performed all health assessments at enrollment in the main trial. Enrollment and procedures of the main trial were supervised by V. A. D., S. B. S., S. M. R., A. B. F., L. D. C., and V. A. D. was responsible for the statistical analyses, with help from S. B. S. and A. B. F. All authors contributed to and approved the final version of the article.

Disclaimer. The funding agencies had no role in the study design, data collection, data analysis, data interpretation, or the writing of the manuscript.

Financial support. This work was supported by the Augustinus Foundation; the Lundbeck Foundation; the Dagmar Marshall Foundation; the Danish Council of Independent Research; the Danish Ministry of Higher Education and Science (DFF-1333-00192); the Søren Segel and Johanne Wilbroe Segel Research Foundation; the European Research Council (ERC-2009-StG to C. S. B.; grant 243149 in support of the main trial); the Danish National Research Foundation (grant DNRF108 in support of the main trial); the Danish Council for Development Research, Ministry of Foreign Affairs (grant 104.Dan.8.f. in support of investigations of nonspecific effects of vaccines), the Novo Nordisk Foundation (in support of nonspecific effects of vaccines), and European Union FP7 support for OPTIMUNISE (grant Health-F3-2011-261375 in support of nonspecific effects of vaccines).

Potential conflicts of interests. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Aaby P, Martins C, Garly ML, et al. Non-specific effects of standard measles vaccine at 4.5 and 9 months of age on childhood mortality: randomised controlled trial. *BMJ* 2010; 341:c6495–c.
2. Aaby P, Bhuiya A, Nahar L, Knudsen K, de Francisco A, Strong M. The survival benefit of measles immunization may not be explained entirely by the prevention of measles disease: a community study from rural Bangladesh. *Int J Epidemiol* 2003; 32:106–16.
3. Aaby P, Samb B, Andersen M, Simondon F. No long-term excess mortality after measles infection: a community study from Senegal. *Am J Epidemiol* 1996; 143:1035–41.
4. Lund N, Andersen A, Hansen AS, et al. The effect of oral polio vaccine at birth on infant mortality: a randomized trial. *Clin Infect Dis* 2015; 61:1504–11.

5. Aaby P, Benn C, Nielsen J, Lisse IM, Rodrigues A, Ravn H. Testing the hypothesis that diphtheria-tetanus-pertussis vaccine has negative non-specific and sex-differential effects on child survival in high-mortality countries. *BMJ Open* **2012**; 2:pii:e000707. doi:10.1136/bmjopen-2011-000707.
6. Aaby P, Ravn H, Benn CS. The WHO review of the possible non-specific effects of diphtheria-tetanus-Pertussis vaccine. *Pediatr Infect Dis J* **2016**; 35:1247–57.
7. Expanded programme on immunization. The optimal age for measles immunization. *Wkly Epidemiol Rec* **1982**; 57:89e91 1982.
8. Martins CL, Benn CS, Andersen A, et al. A randomized trial of a standard dose of Edmonston-Zagreb measles vaccine given at 4.5 months of age: effect on total hospital admissions. *J Infect Dis* **2014**; 209:1731–8.
9. Veirum JE, Sodemann M, Biai S, et al. Routine vaccinations associated with divergent effects on female and male mortality at the paediatric ward in Bissau, Guinea-Bissau. *Vaccine* **2005**; 23:1197–204.
10. UNICEF, WHO. Immunization summary—a statistical reference containing data through 2010. **2012**:71.
11. Plotkin SA, Orenstein WA, Offit PA. *Vaccines*. 5th ed. Philadelphia, Pennsylvania: Elsevier Saunders, **2008**:353–98.
12. Fisker AB, Bale C, Jorgensen MJ, et al. High-dose vitamin A supplementation administered with vaccinations after 6 months of age: sex-differential adverse reactions and morbidity. *Vaccine* **2013**; 31:3191–8.
13. Aaby P, Garly ML, Nielsen J, et al. Increased female-male mortality ratio associated with inactivated polio and diphtheria-tetanus-pertussis vaccines: Observations from vaccination trials in Guinea-Bissau. *Pediatr Infect Dis J* **2007**; 26:247–52.
14. Aaby P, Martins CL, Garly ML, et al. Measles vaccination in the presence or absence of maternal measles antibody: impact on child survival. *Clin Infect Dis* **2014**; 59:484–92.
15. Mina MJ, Metcalf CJ, de Swart RL, Osterhaus AD, Grenfell BT. Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality. *Science* **2015**; 348:694–9.
16. SAGE non-specific effects of vaccines Working Group. Evidence based recommendations on non-specific effects of BCG, DTP-containing and measles-containing vaccines on mortality in children under 5 years of age. Background paper for SAGE discussions. World Health Organization, **2014**.
17. Sorup S, Benn CS, Poulsen A, Krause TG, Aaby P, Ravn H. Live vaccine against measles, mumps, and rubella and the risk of hospital admissions for nontargeted infections. *JAMA* **2014**; 311:826–35.
18. Aaby P, Ibrahim SA, Libman MD, Jensen H. The sequence of vaccinations and increased female mortality after high-titre measles vaccine: trials from rural Sudan and Kinshasa. *Vaccine* **2006**; 24:2764–71.
19. Martins C, Bale C, Garly ML, et al. Girls may have lower levels of maternal measles antibodies and higher risk of subclinical measles infection before the age of measles vaccination. *Vaccine* **2009**; 27:5220–5.
20. Kleinnijenhuis J, Quintin J, Preijers F, et al. Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. *Proc Natl Acad Sci USA* **2012**; 109:17537–42.
21. Ovsyannikova IG, Reid KC, Jacobson RM, Oberg AL, Klee GG, Poland GA. Cytokine production patterns and antibody response to measles vaccine. *Vaccine* **2003**; 21:3946–53.
22. Smedman L, Joki A, da Silva AP, Troye-Blomberg M, Aronsson B, Perlmann P. Immunosuppression after measles vaccination. *Acta Paediatr* **1994**; 83:164–8.
23. Hussey GD, Goddard EA, Hughes J, et al. The effect of Edmonston-Zagreb and Schwarz measles vaccines on immune response in infants. *J Infect Dis* **1996**; 173:1320–6.
24. Schnorr JJ, Cutts FT, Wheeler JG, et al. Immune modulation after measles vaccination of 6–9 months old Bangladeshi infants. *Vaccine* **2001**; 19:1503–10.
25. Rager-Zisman B, Bazarsky E, Skibin A, et al. Differential immune responses to primary measles-mumps-rubella vaccination in Israeli children. *Clin Diagn Lab Immunol* **2004**; 11:913–8.
26. Ziola B, Smith RH. T cell cross-reactivity among viruses of the paramyxoviridae. *Viral Immunol* **1987**; 1:111–9.
27. Weber MW, Milligan P, Sanneh M, et al. An epidemiological study of RSV infection in the Gambia. *Bull World Health Organ* **2002**; 80:562–8.
28. Sorup S, Benn CS, Stensballe LG, Aaby P, Ravn H. Measles-mumps-rubella vaccination and respiratory syncytial virus-associated hospital contact. *Vaccine* **2015**; 33:237–45.
29. Measles vaccines: WHO position paper. *Wkly Epidemiol Rec* **2009**; 84:349–60.